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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,427	07/17/2008	Masashi Isozaki	1029650-000178	2940

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
04/19/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/594,427	ISOZAKI ET AL.	
	Examiner	Art Unit	
	JD SCHULTZ	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *7-9,13 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,10-12 and 14-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *originally* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See action*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I and the species phosphatidylcholine, PEG, and doxorubicin hydrochloride in the reply filed on December 22, 2009 is acknowledged. The traversal is on the ground(s) that there is a special technical feature shared by invention of the claims, which is asserted to be the liposome vehicle. Applicants also assert that the claims listed are generic to the species. This is not found persuasive because these arguments do not address the fact that the liposome vehicle which allegedly links the Groups had art cited by the previous examiner as being taught in the art, which is adequate grounds for breaking unity of invention. Furthermore, the issue of whether the claims are generic to the species does not address the basis of the finding of lack of unity, which asserts that the phospholipids, hydrophilic macromolecules, and drugs do not share a common core structure. The requirement is still deemed proper and is therefore made FINAL.

Claim 18 and claims 7, 8, 9, which do not read on the elected phosphatidylcholine, and claim 13, which does not read on the elected PEG, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on December 22, 2009. Applicants have not complied with the requirement to list those claims which applicants believe read on the elected species (see restriction requirement mailed 11/20/2009, page 4). In an effort to promote compact prosecution, the instant action has been issued based on the determination of which claims read

on the elected species. Should applicants disagree with this assessment, applicants are invited to furnish evidence or reasoned statements as to why such claims are embrace the elected species.

Information Disclosure Statement

The information disclosure statements (IDS's) submitted on April 29, 2009, and December 20, 2006 were filed before the mailing date of the instant first action on the merits. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner, and signed and initialed copies are enclosed herewith.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 10-12, and 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haragai et al. (Pharmaceutical Research Volume 18, Number 9 / September, 2001, pages 1284-1290), in view of Mayer et al. (U. S. Patent Number 5,616,341).

The claims of the instant invention are drawn to a liposome preparation comprising a unilamellar vesicle formed from a lipid bilayer comprising a phospholipid as the main membrane component, and an interior aqueous phase in the vesicle at a pH of up to 5, wherein the liposome has a drug loaded therein, and wherein the vesicle is modified with a hydrophilic macromolecule only on its exterior surface, or the liposome preparation according to claim 1, wherein the drug is the one which is unstable at a pH higher than 5, or wherein the drug loaded is at a concentration of 0.05 mole / mole lipid, or wherein the drug loaded is at a concentration of 0.1 mole / mole lipid, or wherein the main membrane component is a phospholipid having a phase transition temperature of at least 50°C, or wherein the phospholipid is a hydrogenated phospholipid.

The invention also comprises the liposome preparation according to claim 1 wherein the lipid bilayer further comprises a basic compound containing a group selected from amino group, amidino group, and guanidino group as its component, or wherein the basic compound is 3,5-dipentadecyloxybenzamidine hydrochloride, or wherein the hydrophilic macromolecule is polyethylene glycol having a molecular weight of 500 to 10,000 Dalton, or wherein the , or wherein the liposome preparation has an average size of 40 to 140 nm, or 50 to 130 nm, or 60 to 120 nm. The invention also comprises the liposome preparation according to claim 1, wherein the interior aqueous phase has a pH of 2 to 5.

Haragai et al teach a liposome preparation comprising a unilamellar vesicle formed from a lipid bilayer comprising a phospholipid as the main membrane component, wherein the

liposome has rhodamine loaded therein, and wherein the vesicle is modified with a hydrophilic macromolecule only on its exterior surface which is PEG, wherein the compound comprises 3,5, 3,5-dipentadecyloxybenzamidine hydrochloride, and wherein the drug loaded is at a concentration of 0.02 mole / mole lipid, wherein the main membrane component is a phospholipid having a phase transition temperature of at least 50°C, and wherein the phospholipid is a hydrogenated phospholipid. Haragai also teaches liposome preparations having an average size of 100 nm.

Haragai does not teach the liposomes having an interior aqueous phase in the vesicle at a pH of up to 5, or wherein the drug is the one which is unstable at a pH higher than 5, or wherein the drug loaded is at a concentration of 0.1 or .5 mole / mole lipid.

Mayer et al. teaches liposomes comprising phosphatidylcholine having an interior aqueous phase at a pH of up to 5, which carries doxorubicin, which in order for the instant invention to be considered enabled, is unstable at a pH higher than 5.

Neither Mayer nor Haragai et al teach the drug loaded at a concentration of 0.1 mole / mole lipid.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate phosphatidylcholine into the liposomes of Haragai et al. since phosphatidylscholine is a well known phospholipid commonly used in the formulation of liposomes, as evidenced by its use in the liposomes of Mayer et al. The use of phosphatidylcholine is considered to be an art recognized equivalent and its use is considered to be one that would be reached in the process of routine optimization. Furthermore it would have been obvious to use such phosphatidyl containing low pH liposomes in the delivery of

doxorubicin, since doxorubicin is a well-known anticancer treatment, the liposomal delivery of which (at a low pH) is evidenced by Mayer et al. Haragai et al. also teach that their liposomes are effective delivery vehicles for many types of molecules. Finally, it would have been obvious to one of ordinary skill in the art to load the doxorubicin of Mayer et al at .1 or .5 mole/mole, since these amounts are within the range of amounts that would be reached upon the practice of routine optimization.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting

ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 10-12, and 14-17 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 5,676,971, in view of Haragai et al. (Pharmaceutical Research Volume 18, Number 9 / September, 2001, pages 1284-1290), and Mayer et al. (U. S. Patent Number 5,616,341). Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims are drawn to pegylated liposomes, which embrace the scope of the instant claims drawn to pegylated liposomes that have a pH up to 5, and contain doxorubicin. Although the patented claims to not teach liposomes that have a pH up to 5, and contain doxorubicin, this feature is disclosed above in the combinations of Haragai and Mayer et al. as described above. Mayer et al. teaches liposomes comprising phosphatidylcholine having an interior aqueous phase at a pH of up to 5, which carries doxorubicin, which in order for the instant invention to be considered enabled, is unstable at a pH higher than 5. Haragai et al. teach the use of 3,5 pentadecyloxybenzamadine containing liposomes as taught above.

It would have been obvious to use 3,5 pentadecyloxybenzamadine-containing liposomes as taught by Haragai et al. with low pH interiors in the delivery of doxorubicin as taught by

Mayer et al., since doxorubicin is a well-known anticancer treatment, the low pH liposomal delivery of which is also well known, as evidenced by Mayer et al.

Conclusion

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JDS